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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,521	08/23/2002	Mikael Simons	100564-00111	7321

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,521	SIMONS ET AL.	
	Examiner	Art Unit	
	Traviss C. McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22,24-30 and 32-44* is/are pending in the application.

4a) Of the above claim(s) *9-12 and 32-40* is/are withdrawn from consideration.

5)☒ Claim(s) *43 and 44* is/are allowed.

6)☒ Claim(s) *1-8,13-19,22,24-30,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed July 26, 2005 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 2 and 15 have been amended.

Claims 43-44 have been added

Claims 9-12 and 32-40 are withdrawn.

Claims 20-21, 23, and 31 have been canceled.

Remarks drawn to rejections of Office Action mailed March 29, 2005 include:

112 1st paragraph rejection: which has been maintained for reasons of record.

112 2nd paragraph rejections: which have been overcome in part by applicant's amendments and have been withdrawn in part.

An action on the merits of claims 1-8, 13-19, 22, 24-30, and 41-44 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 13-19, 22, 24-30, and 41-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of cholesterol sulfate, GM_1 or bbG, does not reasonably provide enablement for the use of the broad list of compounds as set forth in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 1 is drawn to a method of modulating the sphingolipid-cholesterol microdomain in a patient by administering various substituted gangliosides or cholesterol derivatives. Claim 2 is drawn to a method of influencing the location of components on the sphingolipid-cholesterol

microdomain by administering various substituted gangliosides or cholesterol derivatives. Claims 3-6 provide that various proteins are affected by the method of claim 2. Claim 7 provides that one of various gangliosides are administered. Claim 8 provides that a cholesterol derivative is administered. Claim 13 provides that a ganglioside is administered. Claim 15 provides that 3-30 mg of active agent are administered. Claims 16-19, 22, 24-25, and 30 provide various gangliosides which are to be administered. Claims 26-29 provide various cholesterol derivatives which are to be administered. Claims 41-42 limit the oligopeptide of claim 1.

The state of the prior art

Sphingolipid-cholesterol microdomains, or rafts, are known in the art to be lateral arrangements of specific lipids (including sphingolipids, gangliosides and cholesterol) and also include proteins and other agents (see Simons et al., Nature, vol 387, 1997, 569-72).

The level of predictability in the art

The examiner acknowledges the probability and predictability that certain agents, such as cholesterol sulfate, GM_1 and bbG have efficacy as the active agent, however the art is silent with regard to the predictability of any of the claimed gangliosides or cholesterol derivatives as claimed have the efficacy as instantly asserted, especially in view of the fact that Rietveld et al. shows that cholesterol itself had opposite effects as applicants did.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been

provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy instantly asserted using a compound from the broad group of the independent claims.

The existence of working examples

The working examples set forth in the instant specification are directed to the use of gangliosides BB_1 and bbG and the cholesterol derivative cholesterol sulfate. There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that any compound as claimed would indeed provide the efficacy as instantly asserted.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any of the broad recitation of compounds in the methods as asserted without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. One skilled in the art would be confronted with an undue burden of experimentation to isolate/manufacture, characterize, and test the various compounds of the claims to determine if indeed they have efficacy as asserted.

Applicant's arguments filed on July 26, 2005 have been considered but are not found to be persuasive. Applicants argue that their invention increases the detergent solubility of protein associated with sphingolipid-cholesterol by adding gangliosides, ganglioside derivatives, or cholesterol derivatives and that this finding is surprising in view of the fact that when adding cholesterol, the opposite effect occurs. Applicants arguing that unexpected and divergent results

occur when two closely related molecules are administered is seen to strengthen the examiner's position that undue experimentation would be required to practice the instant invention. If unexpected results occur with these 2 closely related molecules, then it is also logical to believe that unexpected and divergent results could occur between other members of the genus claimed which have not been tested. Applicants also provide various references which show that other members of the claimed genus are shown to work as claimed. It is noted that the references submitted were published after the filing date of the instant application, and thus are not prior art. As such, after the instant application was filed, other groups had to resort to further and undue experimentation to determine whether various members of the genus have the efficacy as instantly asserted. It is noted that these references also state that "we found that natural variations in the double bond structure of the aliphatic side chain can modulate domain formation by sterols. We also found that sphingolipid structure strongly influences domain formation" (citation number 4 of IDS filed - Xu et al., page 33540, right column). Xu et al. further add that "different natural sterols do not promote raft formation to the same extent. In particular, sterols that have a double bond in the B ring promote domain/raft formation more strongly than cholesterol" (column 1 of page 33545) and "domain formation was also dependent on the structure of the sphingolipid component" (column 2 of page 33545).

Claims 1-8, 13-19, 22, 24-30, and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly amended claim 1 provides that a ganglioside or cholesterol derivative selected from the group consisting of "and **cholesterol molecules to which organic groups are added or substituted on the OH function** and which is formed from cholesterol in only one reaction step", which is seen to be indefinite. It is unclear as to what the metes and bounds are to said cholesterol molecule. One of skill in the art would not be able to determine the metes and bounds of the claim as there is no indication of what is to be derivatized on the OH function. Applicants should claim the compounds administered. Stating that the compound administered is a cholesterol molecule which has had an organic group added on the OH function does not clearly define the metes and bounds of the claim. Defining the organic groups intended to be encompassed by the instant claims would obviate this rejection. All claims containing the same phrase are rejected for the same reasons, including claims 2 and 15.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Conclusion

Claims 43 and 44 are allowable. The prior art is not seen to teach or fairly suggest a method of modulating the sphingolipid-cholesterol microdomain in a patient by administering cholesterol sulfate, GM_1, or bbG in an amount effective to increase the detergent solubility of the proteins associated with the sphingolipid-cholesterol microdomain. The closest prior art is seen to be Rietveld et al. who teaches the administration of cholesterol, which has an effect of stabilizing the microdomains.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
January 20, 2006

James O. Wilson
Supervisory Patent Examiner
Art Unit 1624